Aversive properties of naloxone in morphine-treated rats

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Rats have been found to reject distinctively flavoured solutions when their consumption on earlier occasions has been followed by poison or radiation-induced illness (Revusky & Garcia, 1970). The poison or radiation is, therefore, defined as an aversive stimulus. This phenomenon has been used to assess the abstinence syndrome precipitated by naloxone in rats chronically treated with morphine.

Rats were allowed access to distilled water between 1 and 2 p.m. daily; no fluid was available at other times. After adaptation to this regime, a saccharin solution was made available instead of distilled water on every third day. Each presentation of saccharin was followed immediately by administration of naloxone hydrochloride or isotonic saline. For 10 days prior to the first presentation of saccharin, and throughout the rest of the experiment, intraperitoneal injections of either morphine hydrochloride or saline were given twice daily (9.30 a.m. and 5.30 p.m.).

In control rats (n = 8) receiving saline twice daily, three pairings of saccharin solution (0.1%) with naloxone (10 mg/kg i.p.) failed to induce any reduction in the intake of saccharin. In rats (n = 8) receiving morphine (10 mg/kg i.p. twice daily), a single pairing of saccharin with naloxone reduced the mean intake of saccharin from 11.0 ml to 3.0 ml: after three pairings, saccharin intake was 0.6 ml. The intake of distilled water on the days between saccharin presentations was slightly increased ($P < 0.05$), possibly as compensation for the reduced fluid intake when saccharin alone was available. In a second experiment, saccharin was replaced by sodium saccharin, for which rats have a greater preference. The dose of morphine was reduced to 5.0 mg/kg twice daily. A single pairing with naloxone (10 mg/kg i.p.) reduced the mean intake of sodium saccharin solution (0.1%) from 22.0 ml to 9.0 ml (n = 6, $P < 0.001$). The intake of distilled water was not suppressed. When the same doses of morphine or naloxone were given separately to different rats, neither drug affected sodium saccharin intake (n = 6 in each case). Naloxone was, therefore, an aversive stimulus for rats chronically treated with morphine. Analogous results have been obtained with rhesus monkeys, which learned to press keys to delay infusions of naloxone through implanted venous catheters (Goldberg, Hoffmeister, Schlichting & Wuttke, 1971). Doses of naloxone which were effective aversive stimuli in our experiments also produced signs of mild morphine abstinence, such as defaecation and occasional writhing or weight loss.

The conditioned aversion technique makes possible reliable, objective assessments of abstinence precipitated from low doses of morphine; for example, significant ($P < 0.001$) aversions to sodium saccharin were detected in rats receiving doses of morphine as low as 1.0 mg/kg twice daily. With traditional techniques, experimenters have frequently found it necessary to administer very large doses of morphine in order to produce measurable abstinence signs.

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